Pediatric Blood & Cancer / Volume 66, Issue 8

RESEARCH ARTICLE | Open Access

Invasive mold disease of the central nervous system in children and adolescents with cancer or undergoing hematopoietic stem cell transplantation: Analysis of 29 contemporary patients

Melchior Lauten, Andishe Attarbaschi, Gunnar Cario, Michaela Döring, Olga Moser, Urs Mücke, Fiona Poyer, Sarah Rieken, Christian Temme, Sebastian Voigt, Thomas Lehrnbecher, Andreas H. Groll

First published: 07 May 2019
https://doi.org/10.1002/pbc.27806
Cited by: 1

Funding information:

The study was supported by an unrestricted grant by the Elfriede-Haaren-Stiftung, Lübeck, Germany.

T.L. and A.H.G. contributed equally to this article.

This study has not been published as a meeting abstract. However, parts of the results were presented at the

- XV. INFOCUS meeting, November 2017, Curitiba, Brazil
- 29th annual meeting of the international BFM study group, May 2018, Helsinki, Finland
- "MSD pediatric workshop," June 2018, Frankfurt, Germany
- 52nd Scientific Meeting of the German-speaking Mycological Society, October 2018, Innsbruck, Austria

Abstract

Background

Invasive mold disease (IMD) is a severe infectious complication in immunocompromised patients. The outcome of central nervous system (CNS) IMD is poor, but contemporary data, in particular in the pediatric setting, are lacking.

Procedure

For this retrospective multicenter analysis, pediatric patients < 18 years with proven or probable CNS IMD receiving chemotherapy or undergoing allogeneic HSCT were reported by the local investigator. CNS IMD had to be diagnosed between 2007 and 2016. Proven CNS IMD was defined as compatible CNS imaging findings and macroscopic autopsy findings in conjunction with a positive microscopic or microbiological result in CNS tissue or cerebrospinal fluid. Probable CNS IMD was defined as compatible CNS imaging findings in combination with proven or probable IMD at a site outside the CNS.

Results and conclusions

A total of 29 patients (median age, 14 years; 14 allogeneic HSCT recipients) were diagnosed with proven (*n* = 12) or probable (*n* = 17) CNS IMD. *Aspergillus spp*. was the most common fungal pathogen. All but one patient had IMD sites outside the CNS and eight patients (27.6%) were neurologically asymptomatic at diagnosis of CNS IMD. Forty-nine percent of the patients survived CNS IMD; however, 46.7% of the survivors suffered from severe long-term neurological sequelae. Our data suggest that (1) outcome of CNS IMD has improved in children as compared with previous series, (2) half of surviving patients suffer from severe neurological sequelae, and (3) imaging of the CNS should be performed in all children with IMD irrespective of neurological symptoms.

Abbreviations

ALL
: acute lymphoblastic leukemia

CNS
: central nervous system

CSF
: cerebrospinal fluid

HSCT
: hematopoietic stem cell transplantation

IMD
: invasive mold disease

OD
: optical density

PCR
: polymerase chain reaction

SPSS
: Statistical Package for the Social Sciences

1 INTRODUCTION

Invasive mold disease (IMD) may occur in immunocompromised patients, in particular in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), or patients with acute leukemias, leukemia relapse or primary immunodeficiency syndromes.[1-3] The most important pathogen causing IMD in children and adolescents with cancer or undergoing allogeneic HSCT is *Aspergillus spp*., but recent studies report an increasing proportion of non-Aspergillus molds such as Fusarium, Scedosporium, and the Mucorales.[4, 5] Primary sites of IMD are mainly the lungs and the paranasal sinuses, from where the infection may disseminate either hematogenously or by continuous invasion predominantly to the central nervous system (CNS).[2, 5-9] Patients with CNS IMD are difficult to manage, and treatment strategies may differ from IMD of other organs with regard to the choice and dosage of antifungal agent and the need for surgical interventions. A systematic review of the literature reported on 90 children treated for CNS aspergillosis between 1955 and 2005,[10] but there is a lack of contemporary data in the pediatric population. Such data, however, are important not only because diagnostic tools including imaging and biomarkers have improved considerably over the last decade, but also bec and potent antifungal compounds have become available. Voriconazole, for instance, has become the f of choice for CNS aspergillosis, even though it was first approved in 2002 and only recently achieved a p label. We therefore initiated a multicenter analysis including ten pediatric oncology centers from Germany (*n* = 9) and Austria (*n* = 1) to analyze contemporary cases of CNS IMD in immunocompromised children and adolescents with focus on clinical presentation and outcome.

2 PATIENTS AND METHODS

2.1 Patients

For this retrospective multicenter analysis, patients were identified by voluntary reporting of the local investigators. Pediatric patients receiving chemotherapy for an underlying malignancy or patients undergoing allogeneic HSCT were included in the study. Inclusion criteria were proven or probable CNS IMD diagnosed between 2007 and 2016 and age younger than 18 years at the time of diagnosis of CNS IMD. Patients with possible CNS IMD were not included into the analysis. Informed consent was obtained from living patients and/or their parents. Data of patients who had deceased were locally anonymized and transferred into the central database. The study was reviewed and approved by the Ethics Committee of the University of Lübeck (vote no. 15-301).

2.2 Definitions

In accordance with current definitions,[11], [12] proven CNS IMD was diagnosed by compatible CNS imaging[6], [13], [14] or macroscopic autopsy findings in conjunction with a positive microbiological result in the brain tissue or cerebrospinal fluid. Positive microbiological results included a positive culture, microscopic evidence of hyphae, a positive result of the galactomannan assay (OD > 0.5) or detection of a mold spp. by polymerase chain reaction (PCR).[6], [13] Probable CNS IMD was defined as compatible CNS imaging findings in combination with proven or probable IMD at a site outside the CNS in the absence of a plausible alternative diagnosis.[8] Possible disease was stratified as negative disease.

2.3 Analysis

Clinical, imaging, and microbiological data were collected in a standardized pseudonymized data file and transferred into an SPSS database (version 22.0). Most data were analyzed in a descriptive way. The log-rank test was used for survival analysis, and the Pearson χ^2 test was used for analysis of categorical data. *P* values < 0.05 (two-tailed) were considered statistically significant.

3 RESULTS

Twenty-nine pediatric patients (20 males and 9 females) with proven (*n* = 12) or probable (*n* = 17) CNS IMD were included in the study. The demographics of the patients are provided in Table 1. Fifteen patients developed CNS IMD while receiving chemotherapy, whereas 14 were immunocompromised allogeneic HSCT recipients. Underlying conditions included acute lymphoblastic leukemia (ALL; *n* = 16), recurrent ALL (*n* = 5), acute myeloid leukemia (*n* = 2), T-lymphoblastic lymphoma, chronic myeloid leukemia, myelodysplastic syndrome, Ewing sarcoma, chronic granulomatous disease, and severe combined immunodeficiency syndrome (*n* = 1 each). The median age at the time of diagnosis of the underlying disease or HSCT, respectively, was 14.0 years (range, 1.0–18.0). The median age at diagnosis of CNS IMD was 14.0 years (range, 3.0–18.0). Twenty-one of the 29 patients (72.4%) were older than 9 years when CNS IMD occurred. Twenty-two of the 29 patients (75.9%) had received glucocorticoids and/or other immunosuppressive drugs up to one week prior to diagnosis of CNS IMD.

Table 1. Clinical characteristics of the study population (*n* = 29)

		All patients	Allogeneic stem cell transplantation (HSCT)

		All patients		Allogeneic stem cell transplantation (HSCT)	
		N	%	*N*	%
Gender	Female	9	31	3	21
	Male	20	69	11	79
Underlying conditions	Acute lymphoblastic leukemia	16	55	3	21
	Recurrent acute lymphoblastic leukemia	5	17	5	36
	Acute myeloid leukemia	2	7	2	14
	Chronic myeloid leukemia	1	3	1	7
	Myelodysplastic syndrome	1	3	1	7
	T-lymphoblastic lymphoma	1	3	—	—
	Ewing sarcoma	1	3	—	—
	Chronic granulomatous disease	1	3	1	7
	Severe combined immunodeficiency	1	3	1	7
Age at diagnosis of IMD	<2 years	1	3	—	—
	2–9 years	8	28	4	29
	>9 years	20	69	10	71
Neutrophils[a,b]	<500/μL at diagnosis of IMD	4	14	2	14
Immunosuppressive drugs at diagnosis of IMD[c]	Glucocorticoids	20	69	10	71
	Other immunosuppressive drugs	8	28	6	43
	No immunosuppression	5	17	2	14
	No information	2	7	—	—

[a] "All patients" cohort: 11 patients missing.

[b] HSCT cohort: 2 patients missing.

[c] Please note that patients may have received more than one immunosuppressive drug. Immunosuppressive drugs included mycophenolate-mofetil (*n* = 3), cyclosporin A (*n* = 2), tacrolimus, methotrexate, sirolim blinatumomab, and infliximab (one each).

Pathogens identified included *Aspergillus fumigatus* (*n* = 14, *n* = 8 identified by culture of sampled tissue and *n* = 14 by PCR of organ tissue sample, blood or CSF, respectively), *Fusarium spp., Rhizopus arrhizus, Rhizomucor*

pusillus and *Absidia corymbifera* (one case each). In one patient, two pathogens were detected by culture. In 12 patients, the pathogen could not be identified by PCR or culture.

Twenty-one (72.4%) patients presented with CNS-related symptoms at the onset of CNS IMD and eight (27.6%) patients were neurologically nonsymptomatic. Somnolence (n = 7), cerebral palsies (n = 7), and severe headache (n = 6) were frequently reported, whereas impaired vision, aphasia, ataxia, hallucination, paresthesia, seizures, and death due to raised intracranial pressure were reported only for single patients. Symptoms indicating CNS IMD did not influence the time between first diagnosis of IMD and diagnosis of CNS IMD (P = 0.845). In eight patients, CNS IMD was detected during diagnostic work-up for pulmonary and liver mold disease or during routine CNS imaging for infectious work-up. In 15 (51.7%) patients, the CNS was the organ where IMD was first detected. In one patient (3.4%), CNS IMD was diagnosed at postmortem. The median time between onset of IMD and diagnosis of CNS IMD was 1.0 day (range, 1.0–30.0).

All but one patient (96.6%) had sites of IMD outside the CNS, with the lung being affected in 24 patients (82.8%) and various other organs in 11 patients, respectively (37.9%; Table 2). Possible organ disease was stratified as negative disease. All patients without neurological symptoms had pulmonary IMD.

Table 2. Grading of CNS IMD and IMD of organs outside the CNS

Patient ID	Grade of CNS infection	Grade of infection outside the CNS	Microbiological identification
1019, 1023, 1024	Proven	Proven[a]	*Aspergillus fumigatus*
1005, 1015, 1018, 1021	Proven	Proven[a]	[e]
1002, 1003	Proven	Proven[b]	*Aspergillus fumigatus*
1022	Proven	Proven[c]	*Aspergillus fumigatus*
1011	Proven	Probable[a]	[e]
1027	Proven	Possible[d]	*Aspergillus fumigatus*
1010, 1016, 1034	Probable	Proven[a]	*Aspergillus fumigatus*
1032	Probable	Proven[a]	[e]
1033	Probable	Proven[b]	*Absidia corymbifera*
1030	Probable	Proven[b]	*Aspergillus fumigatus*
1007	Probable	Proven[b]	*Fusarium spp.*
1020	Probable	Proven[b]	*Rhizomucor pusillus*
1001	Probable	Proven[b]	[e]
1004	Probable	Proven[c]	*Aspergillus fumigatus and Rhizopus arrhizus*
1008, 1014	Probable	Proven[c]	*Aspergillus fumigatus*

Patient ID	Grade of CNS infection	Grade of infection outside the CNS	Microbiological identification
1025, 1026, 1028, 1029, 1031	Probable	Probable[a]	—

Notes: *N* = 24 patients showed proven (*n* = 10) or probable (*n* = 14) lung disease. Possible organ disease was classified as negative disease.

[a] Probable/proven lung disease plus possible/no disease of other sites (*n* = 17).

[b] Probable/proven lung disease plus probable/proven disease of other sites (*n* = 7).

[c] Possible/no lung disease plus probable/proven disease of other sites (*n* = 4).

[d] Possible/no lung disease plus possible/no disease of other sites (*n* = 1).

[e] Hyphal structures seen in microscopy.

Nineteen patients (65.5%) had received antifungal prophylaxis and/or empirical therapy within two weeks prior to diagnosis of CNS IMD (mold active: *n* = 14; mold-inactive: *n* = 3, specific information about two patients missing). Information on antifungal treatment within one week after diagnosis of CNS IMD was available for 24 patients. Ten (41.7%) and 14 (58.3%) patients received antifungal monotherapy or combination therapy, respectively. Antifungal therapy included voriconazole in 16 (66.7%) and liposomal amphotericin B in 13 (54.2%) patients. The median duration of antifungal treatment in survivors was 508 days (range, 193–999). Thirteen (44.8%) patients underwent a surgical procedure.

At day 30 after the diagnosis of CNS IMD, 19 (65.5%) patients were alive, and the probability of 2-year survival (2-year pOS) was 48.9% (SE 0.10) after a median follow-up of 383.3 days (range, 0–2,357). Whereas only four out of 14 HSCT recipients showed long-term survival, 11 out of 15 patients not undergoing HSCT survived (2-year pOS 28.6%, SE 0.12, vs 73.3%, SE 0.11, *P* = 0.067; Figure 1). In 13 of the 14 nonsurvivors, the cause of death was related to IMD, whereas one patient died due to progression of the underlying malignancy. Among the 15 survivors, seven developed major neurological sequelae (46.7%; hemi-/quadriplegia *n* = 5; amaurosis, visual impairment, aphasia, and encephalopathy, *n* = 1 each). Whereas there was no significant difference in survival between patients who presented with CNS symptoms (2-year pOS 50.0%, SE 0.11) and those who did not (2-year pOS 46.9%, SE 0.19, *P* = 0.838), neurological sequelae were observed only in those patients initially presenting with neurological symptoms at the diagnosis of CNS IMD (Table 3).

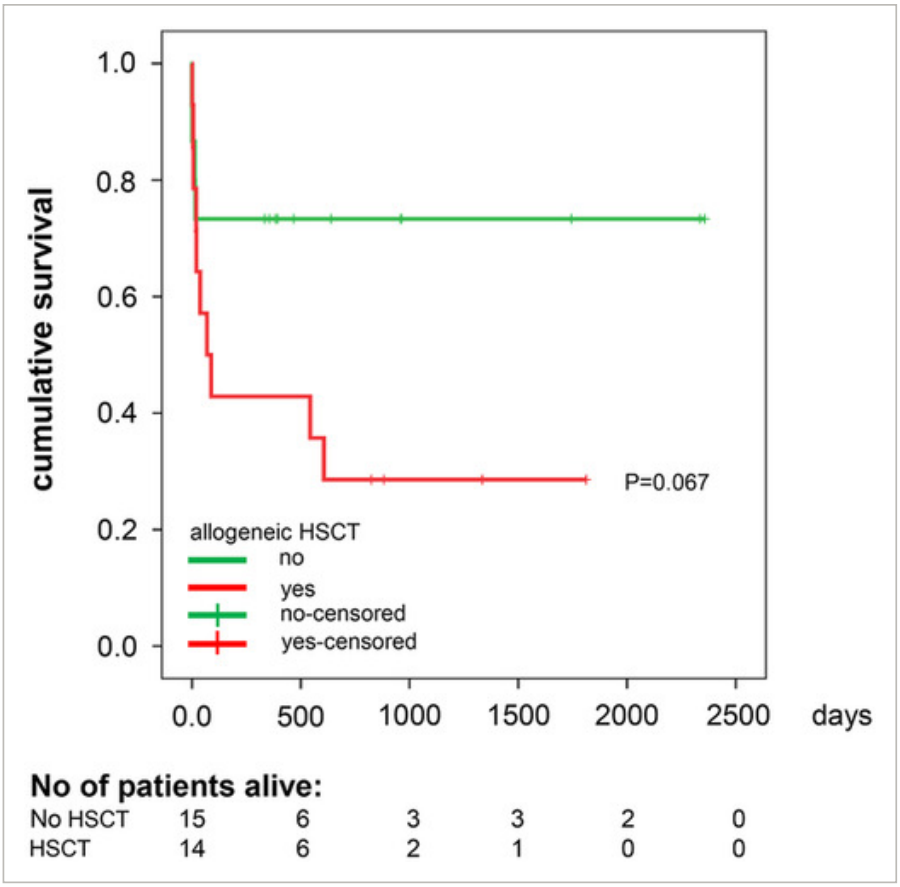

Figure 1

Open in figure viewer | PowerPoint

Cumulative survival of IMD patients with or without allogeneic HSCT

Table 3. Survival and late sequelae in children with invasive mold infection of the CNS

	Neurological symptoms at diagnosis of CNS IMD (*n* = 21)		No neurological symptoms at diagnosis of CNS- IMD (*n* = 8)		All patients (*n*)	
	N	%	*N*	%	*N*	%
Alive	11	52.4[a]	4	50.0[a]	15	100.0
Alive and no late sequelae	4	36.4[b]	4	100.0[b]	8	53.3
Alive and late sequelae	7	63.6[b]	0	—		

Note: Late sequelae were defined as neurologic symptoms not known before CNS IMD.

[a] Percentage of *n* = 21 patients with initial neurological symptoms and *n* = 8 patients without initial neurological symptoms, respectively. No statistically significant difference in survival (*P* = 0.91, two-tailored

Pearson χ^2 test).

[b] Percentage of $n = 11$ surviving patients with initial neurological symptoms and $n = 4$ surviving patients without initial neurological symptoms, respectively.

4 DISCUSSION

The present analysis represents the largest contemporary cohort of pediatric patients with CNS IMD and reveals important differences to previously published studies. For example, a literature review of 90 children treated for CNS aspergillosis between 1955 and 2005 reported that more than half of CNS IMD patients were diagnosed postmortem, whereas in our series, CNS IMD was diagnosed by autopsy in only one of the 29 patients. This difference may be partly explained by the declining number of postmortem examinations,[15] but also by advances in fungal diagnostics, including the advent of sensitive biomarkers and of continuously improving imaging methods. Overall, estimates for the development of CNS IMD in the context of IMD range between 20% and 40%,[5, 7, 8] but robust data are missing, in particular for pediatric patients.

The majority of the patients of our cohort were diagnosed within the age group > 9 years, whereas within the BFM ALL cohort, patients of this age group normally represent not more than 20%.[16] Developing IMD preferably at an older pediatric age corroborates the finding of a previous review on risk factors for invasive fungal disease in children.[1] *Aspergillus spp*. was the most common organism responsible for CNS IMD in our study, which supports previous observations about the distribution of molds causing CNS IMD in severely immunocompromised pediatric patients.[17]

In the present study, the overall survival was 49%, which is similar to the survival rate of a recent series of adult patients,[18] but considerably higher than the overall survival of 35% reported in the review of children with CNS aspergillosis treated between 1955 and 2005.[10] This difference might be explained by the availability of new antifungal agents with potent antimold activity, including (but not limited to) voriconazole.[19] This hypothesis is supported by the observation that survival of patients treated after 1990 has significantly improved as compared to those treated before 1990 (60% vs 18%, $P = 0.01$).[10] However, the estimates of prognosis might be affected by publication bias, as mortality rates in case series are considerably higher as compared with case reports (71% vs 38%).[10]

Survival of our patients was affected by previous treatment, as mortality was significantly higher in allogeneic HSCT recipients than in patients who did not undergo HSCT, which indicates the impact of the net sum of immunosuppression in the development of IMD. Mortality rate was highest during the first 30 days after the diagnosis of CNS IMD. Ten of the 29 patients (34.5%) died during the first 30 days after the diagnosis of CNS IMD, and four died after day 30. Apart from mortality, it is important to note that among the 15 patients surviving CNS IMD, almost half suffered from debilitating long-term neurological sequelae. We found that patients who initially presented with CNS symptoms had a similar overall survival compared to those without CNS symptoms, but long-term sequelae only occurred in those patients with CNS symptoms at diagnosis. This observation supports the intuitive notion that early diagnosis of CNS IMD may improve neurological outcome; however, because this finding is based on a small number of patients, it ultimately remains unclear whether earlier diagnosis of CNS IMD would have improved neurological outcomes in surviving patients. Importantly, more than 20% of the children in our series did not present with neurological symptoms at the time of diagnosis of CNS IMD, and in all these patients, at least one site outside the CNS was affected by IMD, in most patients the lungs. As the diagnosis of CNS involvement might have an important impact on the choice and dosing of antifungal compounds or the consideration of surgery, our data clearly support a previous report suggesting that pediatric patients with the

diagnosis of IMD at any site should undergo a comprehensive diagnostic work-up that includes CNS imaging.[20, 21]

Our study has strengths and limitations. One limitation is the fact that we may have missed patients due to the retrospective study design, and that we did not systematically search available data sets. Thus, unfortunately, our study does not allow providing data on the incidence of CNS IMD in immunocompromised children. A second limitation is the fact that our data may be biased as we only collected data of patients with proven and probable CNS IMD. However, our strict inclusion criteria strengthen the value of data on outcome. In addition, we included data on long-term neurological sequelae in our analysis, which is lacking in most studies. Future prospective studies need to collect data on the true incidence of CNS IMD in patients with IMD outside the CNS, and clarify whether early diagnosis and treatment of CNS IMD will ultimately lead to a better outcome regarding both neurological sequelae and overall survival.

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

REFERENCES

1 Fisher, BT, Robinson, PD, Lehrnbecher, T, et al. Risk factors for invasive fungal disease in pediatric cancer and hematopoietic stem cell transplantation: a systematic review. *J Pediatric Infect Dis Soc*. 2018; **7**(3): 191- 198.
Crossref | PubMed | Web of Science® | Google Scholar

2 Groll, AH, Shah, PM, Mentzel, C, Schneider, M, Just-Nuebling, G, Huebner, K. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect*. 1996; **33**(1): 23- 32.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

3 Roilides, E, Pavlidou, E, Papadopoulos, F, et al. Cerebral aspergillosis in an infant with corticosteroid-resistant nephrotic syndrome. *Pediatr Nephrol*. 2003; **18**(5): 450- 453.
PubMed | Web of Science® | Google Scholar

4 Pana, ZD, Roilides, E, Warris, A, Groll, AH, Zaoutis, T. Epidemiology of invasive fungal disease in children. *J Pediatric Infect Dis Soc*. 2017; **6**(Suppl 1): S3- S11.
Crossref | PubMed | Web of Science® | Google Scholar

5 Zaoutis, TE, Heydon, K, Chu, JH, Walsh, TJ, Steinbach, WJ. Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the United States, 2000. *Pediatrics*. 2006; **117**(4): e711- 716.
Crossref | PubMed | Web of Science® | Google Scholar

6 Schwartz, S, Kontoyiannis, DP, Harrison, T, Ruhnke, M. Advances in the diagnosis and treatment of fungal infections of the CNS. *Lancet Neurol*. 2018; **17**(4): 362- 372.
Crossref | PubMed | Web of Science® | Google Scholar

7 Abbasi, S, Shenep, JL, Hughes, WT, Flynn, PM. Aspergillosis in children with cancer: a 34-year experience. *Clin Infect Dis*. 1999; **29**(5): 1210- 1219.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

8 Denning, DW. Invasive aspergillosis. *Clin Infect Dis*. 1998; **26**(4): 781- 803. quiz 804-785.

Crossref | CAS | PubMed | Web of Science® | Google Scholar

9 Lin, SJ, Schranz, J, Teutsch, SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis*. 2001; **32**(3): 358- 366.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

10 Dotis, J, Iosifidis, E, Roilides, E. Central nervous system aspergillosis in children: a systematic review of reported cases. *Int J Infect Dis*. 2007; **11**(5): 381- 393.
Crossref | PubMed | Web of Science® | Google Scholar

11 Groll, AH, Castagnola, E, Cesaro, S, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. *Lancet Oncol*. 2014; **15**(8): e327- 340.
Crossref | PubMed | Web of Science® | Google Scholar

12 Pauw, B, Walsh, TJ, Donnelly, JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008; **46**(12): 1813- 1821.
PubMed | Web of Science® | Google Scholar

13 Schwartz, S. Diagnostic imaging methods and therapy options for cerebral aspergillosis. *Mycoses*. 2012; **55**(Suppl 2): 10- 16.
Wiley Online Library | PubMed | Web of Science® | Google Scholar

14 Haßler, A, Porto, L, Lehrnbecher, T. Cerebral fungal infection in pediatric cancer patients. *Curr Fungal Infect Rep*. 2015; **9**: 6- 14.
Crossref | Web of Science® | Google Scholar

15 Shojania, KG, Burton, EC, McDonald, KM, Goldman, L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *JAMA*. 2003; **289**(21): 2849- 2856.
Crossref | PubMed | Web of Science® | Google Scholar

16 Moricke, A, Zimmermann, M, Reiter, A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia*. 2010; **24**(2): 265- 284.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

17 Cesaro, S, Tridello, G, Castagnola, E, et al. Retrospective study on the incidence and outcome of proven and probable invasive fungal infections in high-risk pediatric onco-hematological patients. *Eur J Haematol*. 2017; **99**(3): 240- 248.
Wiley Online Library | CAS | PubMed | Web of Science® | Google Scholar

18 Kourkoumpetis, TK, Desalermos, A, Muhammed, M, Mylonakis, E. Central nervous system aspergillosis: a series of 14 cases from a general hospital and review of 123 cases from the literature. *Medicine (Baltimore)*. 2012; **91**(6): 328- 336.
Crossref | PubMed | Web of Science® | Google Scholar

19 Schwartz, S, Ruhnke, M, Ribaud, P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. *Blood*. 2005; **106**(8): 2641- 2645.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

20 Broenen, E, Mavinkurve-Groothuis, A, Kamphuis-van Ulzen, K, Bruggemann, R, Verweij, P, Warris, A. Screening of the central nervous system in children with invasive pulmonary aspergillosis. *Med Mycol Case Rep*. 2014; **4**: 8- 11.

Crossref | PubMed | Google Scholar

21 Pagano, L, Ricci, P, Montillo, M, et al. Localization of aspergillosis to the central nervous system among patients with acute leukemia: report of 14 cases. Gruppo Italiano Malattie Ematologiche dell'Adulto Infection Program. *Clin Infect Dis*. 1996; **23**(3): 628- 630.
Crossref | CAS | PubMed | Web of Science® | Google Scholar

Citing Literature